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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/694,758	10/23/2000	Shukti Chakravarti	021825-004710US	7408

20350 7590 08/20/2008

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
08/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/694,758	CHAKRAVARTI, SHUKTI	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,45-52 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,45-52 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/16/08 has been entered.

Claim Status

2. Claims 1-41, 43, 44, 53, 55 and 56 have been canceled as filed on 5/16/08.

Claims 42, 45-52 and 54 are currently pending

Claims 42, 45-52 and 54 are being examined in this application.

Election/Restrictions

3. Applicant's election of Group IV (original Claims 5-7) as previously acknowledged.

Priority

4. This application claims priority to U.S. Provisional Patent Application No. 60/160,835, filed 10/21/1999.

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or

more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The instant claims recite methods of diagnosing ulcertative colitis (UC) or "Crohn's disease (CD) by determining at least a combination of five genes including "GRO3", "HNL", "MMP-12", "elafin", and "COL6A3". The said provisional application, 60/160,835, does not provide support for the said method of UC or CD diagnosis using the "combination" of specific five genes. The said provisional application only provides a list of various genes that were differentially expressed in different cell types. The said provisional application does not specifically recite any specific "combination" of genes that can be used as markers for the purposes of diagnosis of any particular disease.

Thus, the instant application does not obtain the priority benefit of the provisional application. The effective filing date of the instant claims (42, 45-52 and 54) is 10/23/2000.

Information Disclosure Statement

6. The information disclosure statement filed 5/16/08 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because all the listed references were not provided with date information. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Objection(s) / Rejection(s) Withdrawn

7. In light of applicants' amendment to the claims, the following claim objection as set forth in the previous office action is withdrawn:

A.) Claim 42 is objected to because of the following informalities: The instant claim 42 is missing a proper conjunction (i.e. "and" or "or") in between part (d) and (e) of the said claim. Appropriate correction is required.

8. In light of applicants' amendment to the claims, the following claim rejections as set forth in the previous office action are withdrawn:

A.) Claims 42, 45, 47, 48, 50-52 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (Digestive Diseases and Sciences, Vol. 41, No. 4 (April 1996), pp. 660-669; previously cited), and Poulakkainen (Gastroenterology. 114:A1064; 1998; previously cited).

B.) Claims 42, 45, 47-52 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroeterology, vol 114, No. 4, April 1998; cited previously) and Poulakkainen (G4358; cited previously).

C.) Claims 42, 45, 47-52 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (Digestive Diseases and Sciences, Vol. 41, No. 4 (April 1996), pp. 660-669; previously cited), in view of Poulakkainen (G4358; previously cited) and Dieckgraefe et al (Gastroeterology, vol 114, No. 4, April 1998; cited previously).

D.) Claims 42, 45, 47-52 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

New Claim Objection(s) / Rejection(s)

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter Rejection

10. Claims 42, 45-52 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 42 has been amendment as filed on 5/16/08. Claim 42 as amended recite step (a) determining an expression level of a macrophage inflammatory protein-2β … and type VI collagen α3 chain" and step (c) "associating an increase in the expression level of each of said GRO3…" "with a UC phenotype" , which recites an expression level based on the specific combination of the listed five genes and using the increased gene expression profile of the said five genes for the diagnosis of UC phenotype; the instant claim 42 also specifically claims using the specific combination of the said five genes (with two specific genes overexpress) for the specific diagnosis of CD phenotype. However, the instant specification does not provide support for the "combination" of genes and using the specific combination of genes for the differential diagnosis of the two type of diseases (UC and CD) based on the differential gene expression profiles.

Applicants have listed various citations of the instant specification (Reply, p.5, para 2) for alleged supports of the said claim amendments especially to the instant claim 42. However, the listed citations (i.e. pp.5, 6, 18, 19, Table 1) only provide a general and generic description of gene expression profiles. The citations do not provide specific support for the instant claimed species of the combination of five genes or using the same for the purpose of diagnosing UC and CD. For example, Table 1 of the instant specification only provides a generic list of hundreds of genes that are observed to overexpress in either UC or CD cells compared to normal cells. The instant Table 1 does not provide support for any specific sub-combination or combination of genes that can be used for specific diagnosis of either UC or CD.

If Applicant believes this rejection is in error, applicant must disclose where in the specification support for the entire scope of the amendment(s) and/or new claims can be found. As a result, Claim 42 and its dependent claims represent new matter.

Written Description Rejection

11. Claims 42, 45-52 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained over the newly added claims (42-52), and is also necessitated by applicant's amendments to the claims.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to the decision of The Court of Appeals for the Federal Circuit, which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

The instant claims are drawn to a genus of methods for determining the gene expression level of a gene product in a sample. The instant claims are drawn to a specific combination of five genes (i.e. GRO3, HNL, elafin, COL6A3, and MMP-12). The instant claims are also drawn to compare the expression levels of the said genes, and "associating" the different levels with "IBD" or "pre-IBD" phenotypes. The instant claims are also drawn to using specific sub-combination such as the subcombination of MMP-12 and elafin for the diagnosis of CD (or differentiating CD from UC.

The instant specification does not provide support for "associating an increase in the expression level" of the specific combination the five specific genes, GRO3, HNL, MMP-12, elafin, and COL6A3 to a UC phenotype. The instant specification also does not provide support for "associating an increase in the expression level" of the specific combination the two specific genes, MMP-12 and elafin to a CD (Crohn's disease) phenotype. The instant specification also does not provide support for the specific method of differentiating between UC and CD phenotypes based the said specific combination of five genes. The instant specification does not provide any examples of using the said combination of genes to specifically diagnose UC and/or CD in any subject in vivo.

Using gene expression profile (specifically based on a certain set of genes) for diagnosis of either UC or CD, or distinction between UC and CD is not known in the art. For example,

Warner et al (Inflammatory Bowel Diseases. Vol.8(2): 140-157; 2002; published after the instant filing date) teach using gene expression profiling to distinguish subtypes of UC and/or CD were not "conclusive" (e.g. p.153, left col.), and the genetic basis for the said diseases are not fully understood (e.g. p.140; p.153). In addition, **Wu** et al (Inflammatory Bowel Diseases. Vol.13(7): 807-821; 2007) teaches that "differential gene expression" between UC and CD samples can vary according to the different clinical samples (e.g. p.820, para 2). That is genes showed to be underexpressed in one CD sample can be later shown to be overexpressed in another. Thus, using gene expression profile to distinguish between UC and CD is highly unpredictable. In addition, the Wu reference (published 8 years after the instant effective filing date) teaches numerous genes (more than 5 specific genes) are responsible for the differential gene expression profile between UC and CD samples (e.g. p.820, left col.). Thus, using any of the combination of genes to distinguish or diagnose UC and/or CD is highly unpredictable.

Thus, applicants are not in possession of the claimed method of using the expression profile of five specific genes for the diagnosing UD or CD.

Enablement Rejection

12. Claims 42, 45-52 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims / The nature of the invention

The nature of the invention is a method of diagnosis of UC and/or CD using gene expression profiling of a combination of specific five genes. The instant claims are drawn to a genus of methods for determining the gene expression level of a gene product in a sample. The instant claims are drawn to a specific combination of five genes (i.e. GRO3, HNL, elafin, COL6A3, and MMP-12). The instant claims are also drawn to compare the expression levels of the said genes, and "associating" the different levels with "IBD" or "pre-IBD" phenotypes. The instant claims are also drawn to using specific sub-combination such as the subcombination of MMP-12 and elafin for the diagnosis of CD (or differentiating CD from UC).

The state of the prior art / The predictability or lack thereof in the art

Using gene expression profile (specifically based on a certain set of genes) for diagnosis of either UC or CD, or distinction between UC and CD is not known in the art. For example, **Warner** et al (Inflammatory Bowel Diseases. Vol.8(2): 140-157; 2002; published after the instant filing date) teach using gene expression profiling to distinguish subtypes of UC and/or CD were not "conclusive" (e.g. p.153, left col.), and the genetic basis for the said diseases are not fully understood (e.g. p.140; p.153). In addition, **Wu** et al (Inflammatory Bowel Diseases. Vol.13(7): 807-821; 2007) teaches that "differential gene expression" between UC and CD samples can vary according to the different clinical samples (e.g. p.820, para 2). That is genes showed to be underexpressed in one CD sample can be later shown to be overexpressed in another. Thus, using gene expression profile to distinguish between UC and CD is highly unpredictable. In addition, the Wu reference (published 8 years after the instant effective filing date) teaches numerous genes (more than 5 specific genes) are responsible for the differential gene expression profile between UC and CD samples (e.g. p.820, left col.). Thus, using any of the combination of genes to distinguish or diagnose UC and/or CD is highly unpredictable.

Additionally, the in vitro data provided given the unpredictability of the art would not be viewed as correlative to human applications. In vivo application necessarily involves unpredictability with respect to physiological activity of an asserted process in humans. See discussion in Ex parte Kranz, 19 USPQ2d 1216,1218-1219 (6/90).

The level of one of ordinary skill

The level of skill would be high, most likely at the Ph.D./MD level.

The amount of direction or guidance present / The presence or absence of working examples

The instant specification does not provide support for "associating an increase in the expression level" of the specific combination the five specific genes, GRO3, HNL, MMP-12, elafin, and COL6A3 to a UC phenotype. The instant specification also does not provide support for "associating an increase in the expression level" of the specific combination the two specific genes, MMP-12 and elafin to a CD (Crohn's disease) phenotype. The instant specification also does not provide support for the specific method of differentiating between UC and CD phenotypes based the said specific combination of five genes. The instant specification does not provide any examples of using the said combination of genes to specifically diagnose UC and/or CD in any subject in vivo.

The quantity of experimentation needed

Due to the unpredictabilities of using the specific five genes for specific diagnosis of UC and/or CD as well as the lack of understanding of the genetic basis for IBD diseases, undue experimentation would be required. The art has not demonstrated any combination of genes or the five specific genes can be used to differentially diagnose UC and/or CD. Because the instant specification only provides an in vitro observed gene expression pattern in isolated samples, undue experimentation would be required to practice claimed method of diagnosis in any subject using gene expression profiles.

Conclusion

Therefore based on the evidences as a whole regarding each of the above factors (e.g. factors 1-8), the specification, at the time the application was filed, does not satisfy the

enablement requirement for the instant claimed method. Please note that this is a "scope of enablement" rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Patent Examiner, Art Unit 1639
8/14/08